LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Immunoglobulin response to intravenous streptokinase in acute myocardial infarction

SIR,—Lynch *et al*'s study (*British Heart Journal* 1991;**66**:139–42) contributes to the growing body of information on the immune response after administration of intravenous streptokinase for acute myocardial infarction. The current focus has been on the length of the period during which important titres of antibodies to and neutralising capacity for streptokinase persist (these do not always correlate precisely[2]). Studies by Lynch *et al*[1] and Jalilal and Morris[3] showed that this period extends at least to 12 months, and further work is awaited to determine the outer limit of this period. During this period streptokinase should not be readministered because of fears of an anaphylactic reaction and also that the drug will be neutralised and hence ineffective.

The current recommendations of the *1990–91 Data Sheet Compendium* are that a second dose of streptokinase should not be given within a period of five days to six months after the first. A recent *Drug and Therapeutics Bulletin* states that this will soon be amended to a 12 month interval.[4] Recent authoritative papers[5,6] have been broader in their recommendations, suggesting that streptokinase and anistreplase should not be readministered within a year, and the latter paper[6] concluded with the assertion that tissue plasminogen activator (alteplase) should be used if repeat thrombolysis is required (no time limit was stated so it presumably extended indefinitely from day 0). A policy of not repeating streptokinase for a year from day 0 has been widely adopted. These conclusions are important because alteplase costs ten times as much as streptokinase.

This policy loses sight of the early window that exists before the development of a significant immune response to streptokinase. This is a worthwhile opportunity given that 9% of patients will reinfarct in the first year after thrombolysis.[7] In a substantial number of these patients reinfarction requiring repeat thrombolysis occurs in the first few days after thrombolysis. In White *et al*'s 1990 study of repeat thrombolysis after myocardial infarction 31 patients were treated for recurrent myocardial infarction after thrombolysis between one and 716 days after initial thrombolysis.[5] The median interval was only five days and 10 of the 31 patients were treated in the first three days. Lynch *et al*'s study shows that antibody titres to streptokinase (IgG) do not rise above baseline until day four, suggesting that a significant immune response (either anaphylactic or neutralising) is unlikely before this. The work of Massel *et al* on neutralising antibody showed a neutralising capacity equivalent to $1{\cdot}5 \times 10^6$ units streptokinase between days five and nine in all their patients[8] (this small study (11 patients) may not have adequately defined the normal range). This again suggests that there is an early opportunity to readminister streptokinase safely and effectively. Indeed though White *et al* recommended that streptokinase should not be readministered within a year they did show that readministration within this period was effective (albeit with an increased incidence of minor side effects).

This evidence suggests that streptokinase can be readministered safely and effectively from 0 to 3 days after the initial event. A further large study of neutralising capacity would be helpful because the most recent study dealt only with antibody response and a previous study of neutralising capacity was small. If this policy is adopted as a refinement of the day 0 to one year policy, which seems to be emerging, it is likely to have an impact on coronary care unit drug bills.

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1 Lynch M, Littler WA, Pentecost BL, Stockley RA. Immunoglobulin response to intravenous streptokinase in acute myocardial infarction. *Br Heart J* 1991;**66**:139–42.
2 Moran DM, Standring R, Lavender EA, Harris GS. Assessment of anti-streptokinase antibody levels in human sera using a micro-radioimmunassay procedure. *Thromb Haemost* 1984;**52**:281–7.
3 Jalilal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990; **335**:184–5.
4 *Drug Ther Bull* 1991;**29**:16.
5 White HD, Cross DB, Williams BF, Norris RM. Safety and efficacy of repeat thrombolytic treatment after acute myocardial infarction. *Br Heart J* 1990;**64**:177–81.
6 White H. Thrombolytic treatment for recurrent myocardial infarction. *BMJ* 1991;**302**: 429–30.
7 Rivers JT, White HD, Cross DB, Williams BF, Norris RM. Reinfarction after thrombolytic therapy for acute myocardial infarction followed by conservative management: incidence and effects of smoking. *J Am Coll Cardiol* 1990;**16**:340–8.
8 Massel D, Turpie AGG, Gill JB, Cairns JA, Russett J. Development of neutralizing antibodies after 1·5 million units of streptokinase in the treatment of acute myocardial infarction [abstract]. *Circulation* 1989; **80**(suppl II):350.

This letter was shown to the authors and an advsior, who reply as follows:

SIR,—We are grateful to Dr Grant for his comments. We agree, as stated in our final paragraph, that it would be prudent to avoid repeating the dose between three days and at least one year after the initial treatment with streptokinase. After treatment with streptokinase, the antibody titre (IgG, subclass IgG1) virtually disappears, presumably because the antibody combines with the antigen, streptokinase. Subsequently, there is a gradual rise in antibody titre, which does not become significantly higher than baseline titres until day 4. During this time window of 0–3 days, when antibody titres are no higher than pretreatment titres, it is probably as safe and effective to re-administer streptokinase in the event of a repeat infarction as in the case of the initial infarct.

We are continuing to monitor streptokinase antibody titres in this cohort of 20 patients, who have now reached the 18 month time point. Though they are gradually declining, the mean (SD) IgG titres to streptokinase are still significantly raised at two years (86·42 (102·9)) over baseline titres (14·63 (4) ($p < 0{\cdot}025$). Repeat infarction after 72 hours and until at least 18 months after the initial infarct should probably be managed with a non-streptokinase thrombolytic agent until the significance of these antibodies is known.

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SIR,—Dr Grant raises an interesting point about the possible readministration of streptokinase or streptokinase-containing compounds in the first three days after initial administration. Specific antistreptokinase IgG concentrations initially fall and then increase over this time[1] and there may be an early time window when readministration could be safe and effective. However, the time course of the immunological response varies from patient to patient and individual patients may therefore receive ineffective therapy if this approach is adopted.

Readministration of *effective* thrombolytic therapy is important because reocclusion in the first few days is associated with poor clinical outcome and higher mortality. For example, in the TAMI (thrombolysis and angioplasty in myocardial infarction) trials patients who had an initially patent artery that then reoccluded over the first few days had a significant increase in hospital mortality from 4·5% to 11% ($p = 0{\cdot}01$).[2]

Other thrombolytic agents available such as urokinase or alteplase can be used without raising concern about the effectiveness of readministration. It seems prudent, therefore, not to readminister streptokinase or compounds containing streptokinase in the first few days unless evidence emerges that high titres of antistreptokinase IgG or high neutralisation titres do not compromise safety or efficacy.

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1 Lynch M, Littler WA, Pentecost BL, Stockley RA. Immunoglobulin response to intravenous streptokinase in acute myocardial infarction. *Br Heart J* 1991;**66**:139–42.
2 Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, Sigmon KN, Kereiakes D, George B, Stack R, and the TAMI study group. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990;**82**:781–91.

Myocardial ischaemia and ventricular arrhythmias precipitated by physiological concentrations of adrenaline in patients with coronary artery disease

SIR,—McCance and Forfar (*British Heart Journal* 1991;**66**:316–9) reported the effects of adrenaline on the development of ischaemia and arrhythmia in patients with ischaemic